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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/720,448	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52 and 54-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52 and 54-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 3/9/10 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/10/09 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/9/10 has been entered.

Applicant has added claims 57-64. Therefore, claims 52 and 54-64 are pending in the application.

Applicant's amendments and/or arguments filed on 3/9/10 have been fully considered but are not persuasive for the reasons set forth below.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied

with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application 60/358580 does not teach the following limitations: the sense and antisense strands each comprise 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-flouro, or universal base modifications. The priority document does not each teach these elements in combination with the structural elements of claims 53-56.

Applicant pointed to support for each of the instant claim limitations in PCT/US03/05346 and 60/408,378. Therefore, the instant claims are accorded an effective filing date of 9/5/02, the filing date of application 60/408,378.

The passage that application pointed to on pages 9 and 10 of application 60/358,580 does not disclose "10 or more" of each of the instant modifications, but rather discloses one or more of each. Applicant argues that "one or more" represents a maximum range that clearly comprise the range of "10 or more". Applicant's argument

is not convincing because the specification of each document clearly sets forth many distinct embodiments and does not contemplate interposing these embodiments. Disclosure of "one or more" of a specific type of modification is not supportive for the specific range of "ten or more", which excludes those quantities less than ten.

Applicant points to support for the instant claim limitations in application 60/386,782 on page 10, lines 3-16 and application 60/358,580 (paragraph spanning pages 9 and 10). However, this passage sets forth one embodiment wherein each strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioates and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or one or more universal base modified nucleotide. This embodiment does not support part (d) of instant claims 52 and 59, which requires 10 or more, not one or more, of such modifications, and requires for the modifications to by pyrimidine. The passage discloses another embodiment that requires one or more, more specifically 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides in one or both strands to have 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro modifications, which is not supportive of 10 or more and does not include universal base modifications.

Applicant points to specific species of molecules that fall within the instant genus, which in no way would point one of skill to the instant genus, which is broader than the specific species.

Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim

limitation in each of the claimed priority documents specifically in the combined context as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52 and 54-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Nyce (WO 99/13886), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

The instant claims are directed to a siRNA molecule having a sense and an antisense strand wherein one or both strands comprise 10 or more 2'-deoxy, 2'O-methyl, 2'-deoxy-2'-flouro, or universal base modified nucleotides and the sense strand comprises a terminal cap at one or both ends. The claims are further directed to 10 or more pyrimidines of the sense strand, antisense strand, or both being 2'-deoxy, 2'O-methyl, or 2'-deoxy-2'-flouro; the sense and/or antisense strand comprises

phosphorothioates, and to a composition comprising the siRNA molecule and a pharmaceutically acceptable carrier.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. The siRNAs taught by Elbashir et al. mediated RNAi via RISC. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications that retained activity.

Elbashir et al. teaches that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function (see page 6886, column 2); modifying terminal nucleotides (see page 6881), meeting the instant limitation of a terminal cap; the siRNA molecules comprise ribonucleotides (see Fig. 1, for example); duplexes of 21 nt siRNAs with 2 nt 3'-overhangs were the most efficient triggers of sequence-specific mRNA degradation (see abstract, for example); modification of the overhangs (see page 6881); wherein the siRNA is in a composition with a pharmaceutically acceptable diluent, such as buffer (see Materials and methods, page 6886).

Elbashir et al. do not teach double stranded nucleic acid molecules with combinations of modifications at the instant number of positions and do not teach phosphorothioates.

Elbashir et al. do not teach 2'-deoxy-2'-flouro modifications, although the only claims that require such are claims 58 and 64, as this is just one species of the genus of the remainder of the claims.

Nyce teaches antisense oligonucleotides that attenuate the expression of target mRNA. The oligonucleotides are preferably up to about 30 nucleotides in length, more preferably up to about 21 nucleotides in length (see page 16). Nyce teaches antisense oligonucleotides targeted specifically to human muscarinic acetylcholine receptor 3 (CHRM3) (see page 54). Nyce teaches phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73) for enhancing the uptake of the oligonucleotides. The 100% substituted oligonucleotide comprises a phosphorothioate at the 3' end. Nyce teaches compositions comprising the oligonucleotide and a pharmaceutically acceptable carrier (see page 77). Nyce teaches surfactants or surfactant components bound to the 5' and/or 3' ends or the oligonucleotides for enhancing uptake of the oligonucleotide (see page 80).

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties,

and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications. However, it is noted that the instant claims do not recite any upper length limitation. Furthermore, the extensively modified dsRNA of Parrish et al. resulted in strong RNAi activity.

Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs. Bertrand et al. teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Bertrand et al. teach that siRNA activity, but no antisense oligonucleotide activity, was observed in mice, probably due to the lower resistance to nuclease degradation of antisense oligonucleotides (see abstract). Bertrand et al. teach that siRNAs are composed of small double-stranded RNA oligonucleotides with a length of 21/22 bases (see page 1000, column 1). Bertrand et al. teach that delivery is a very similar issue for both approaches and that siRNAs are very promising tools for gene inhibition *in vivo* (see page 1000, column 2).

Braasch et al. teach that the need for antisense oligomers that are more potent

and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity (see page 4503). Braasch et al. teach goals for improving oligonucleotides including: improve pharmacokinetics, tissue distribution, and targeting; characterize the mechanism of RNA interference and its full potential for inhibition of gene expression for cell culture studies; use RNAi for in vivo inhibition of mammalian gene expression; perform comparative studies to demonstrate the relative strengths of different oligomer chemistries for given applications (i.e. morpholino versus RNAi) (see Table 2). Braasch et al. teach that if good *in vivo* uptake can be achieved, RNAi might significantly improve the ability of oligonucleotides to have an impact (see page 4509).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to synthesize a siRNA with the structural

characteristics taught by Elbashir et al. with modifications within the instant genus and wherein 10 or more pyrimidines are modified with the instant modifications.

Furthermore, it would have been obvious to incorporate each of the instant types of chemical modifications or combinations of chemical modifications, as each of the types of modifications are taught by Elbashir et al., Matulic-Adamic et al., or Parrish et al. to enhance nucleic acid inhibitory molecules.

It would have been obvious to incorporate the modifications differentially between purines or pyrimidines because the genus of possible places to incorporate the known modifications is very small (pyrimidine or purine). When incorporating modifications in nucleic acids, the modifications are incorporated into a purine or a pyrimidine. Given that the modifications were known in the art to benefit nucleic acid stability, and it was known to incorporate the same modifications from antisense/ribozyme technology into siRNAs, wherein the only possible places to incorporate the modifications is on a purine or a pyrimidine, it would have been obvious to incorporate the instant modifications into at least 10 nucleotides of the sense and/or antisense strand in combination with the specific modification of 10 or more pyrimidines and this is considered within the realm of routine optimization.

One would have been motivated to synthesize a siRNA molecule, as taught by Elbashir et al., and to incorporate the modifications of Nyce given that Nyce teaches antisense oligonucleotides and teaches modifications thereof (phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73)) for

enhancing the uptake of the oligonucleotides. Therefore, one would have been motivated to incorporate the same types of modifications into a siRNA for the same purpose of enhancing uptake of the molecule, especially given that Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs and teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Furthermore, Bertrand et al. teach that siRNA technology can be applied in the same delivery situations that have been previously studied with antisense oligonucleotides.

One would have been motivated to incorporate 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. or Matulic-Adamic et al., as well as 2'-O methyl, 2'-deoxy modifications, and phosphorothioates, as taught by Matulic-Adamic et al., as each of these chemical modifications, as well as various combinations of chemical modifications, were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids, as taught by Matulic-Adamic et al. One would have been motivated to incorporate the modifications on purines or pyrimidines as a matter of optimization of the activity of the siRNA, given there are only two choices.

The instant genus is very broad. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules. Due to the breadth of the instant claims, the teachings of Elbashir et al. are considered to be motivation

with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the huge genus of molecules that are being instantly claimed, the teachings of Elbashir et al. are considered to offer motivation to test various types of known chemical modifications at different percentages in order to optimize the activity of the molecule.

It is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see pages 109-110).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Furthermore, Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity. Braasch et al. further recognize that goals to improve RNAi can be accomplished by utilizing chemical modifications. Since Braasch et al. teach that chemical modifications yield more potent and more selective antisense oligomers, such as oligomers for RNAi, and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, the gene expression of Elbashir et al. and Parrish et al. being inhibited by RNAi, one would have been motivated to synthesize duplexes with different levels of modifications to optimize the activity of the molecule.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the

same benefits to RNAi technology.

For example, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Olie et al., into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Nyce, Matulic-Adamic et al., Parrish et al. and Olie et al., wherein each of the molecules face similar delivery challenges, and each of which can be improved with modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for modifications at various percentages to benefit the

double stranded nucleic acid molecules of Elbashir et al.

Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Olie et al. teach experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments--Claim Rejections - 35 USC § 103

Applicant argues the priority date of the instant claims, which has been addressed in the priority section above.

Applicant argues that Elbashir et al. teaches away from modifying more extensively than what is shown in Figure 4 because 50% and 100% modification abolished activity. Applicant continues to drawn conclusions of the teachings of Elbashir et al. that are outside of the data and teachings of Elbashir et al. Elbashir et al. teaches 19% successful modification and teaches that 50% or 100% (one or both full strands) with 2'-deoxy or 2'-O-methyl (one modification only) abolished activity. Elbashir et al. does not teach any other data. Therefore, the only thing that Elbashir et al. teaches away from is 100% modification of one or both strands with 2'-deoxy only or 2'-O-methyl only. None of the instant claims are identical to this teaching and therefore Elbashir et al. does not teach away from the instant claims. Although applicant continues to read the passage on page 6885 of Elbashir et al. out of context, the only "more extensive" modification that could be referred to is the complete modification of one or both strands, as from a full reading of the article is the only modification that was tested outside of the 2 or 4 nucleotides on each end.

It is well recognized in the nucleic acid inhibitor art that some types and levels of modification will yield active molecules, and some will not, thus resulting in a need for routine optimization. Applicant appears to have set forth some type of guideline requiring for every embodiment tested by Elbashir et al. to have resulted in activity. However, Elbashir et al. does teach successful modification, which would motivate one of skill in the art to incorporate modifications and test different levels of modification.

The same types of chemical modifications that have been used routinely in the antisense and ribozyme art have been used in the RNAi art as well and have produced active molecules when routinely optimized.

Elbashir et al. in no way teaches away from the instant claims, which are not commensurate in scope with the 100% modified duplexes that were inactive of Elbashir et al. Elbashir et al. offers motivation to incorporate modifications to reduce the cost of RNA synthesis and to enhance RNase resistance of siRNA duplexes (see page 6885, column 1). The fact that Elbashir et al. is silent as to modification between 19% and 100% would in fact motivate the skilled artisan to modify more extensively than the 19% to optimize the activity/stability balance.

Applicant argues the motivation to extensively modify duplexes, rather than focusing on the instant claim scope. The instant claims require a total of 10 modified positions of out a possible 24 positions. Elbashir et al. teaches successful modification of 8 positions of a duplex, wherein whether the nucleotides are pyrimidine or not would depend on the target sequence, wherein the instant claims are not directed to any specific target. Therefore, the extensive modification that applicant refers to in the context of the instant claims is an addition of 2 modifications when compared to Elbashir et al.

With regards to Parrish, applicant asserts that although Parrish teaches 2'-deoxy-2'-flouro uridines as compatible with RNAi, Parrish does not suggest cytidine modification or modification to short RNA duplexes. It is noted that applicant is arguing a limitation that is not in the claims, as the claims are not directed to cytidine

modification. Furthermore, the 2'-deoxy-2'-flouro uridine modification represents a dsRNA that was extensively modified and acted via RNAi. Although applicant continues to argue elements that are not claimed, applicant has not argued the fact that Parrish teaches a dsRNA with 2'-deoxy-2'-flouro uridine modification that resulted in strong activity. There is no reason to expect that shorter dsRNAs, wherein Parrish itself teaches that duplexes 26bp in length act via RNAi, would not remain active with the same modification, particularly given that the long dsRNA of Parrish was necessarily cleaved via Dicer in the cell into short siRNA molecules in order to be loaded into RISC and be active. Applicant's assertion regarding Parrish teaching away from 2'-deoxy modifications is completely unfounded given that Parrish specifically teaches 2'-deoxy incorporation with strong RNA interference activity. Applicant points to other examples in Parrish where modification of cytidine to deoxycytidine produced a substantial decrease in interference. Importantly, this does not negate that Parrish teaches a dsRNA with 2'-deoxy-2'-flouro uridine modification that resulted in strong activity. Furthermore, it is well known in the RNAi art that there is a need to balance activity and stability. Modifications that decrease activity are often incorporated to enhance stability as long as the molecule is in fact still active. The teaching pointed to by applicant in no way teaches away from pyrimidine modification and is certainly not commensurate in scope with the instant claim breadth.

With regards to the teaching of Parrish specific to phosphorothioate modifications, applicant again is arguing elements that are not claimed, as the instant

broad claims do not require phosphorothioates and even the claims that do require phosphorothioate modifications only require 1 phosphorothioate modification.

Applicant argues that Bertrand teaches a comparison of modified antisense oligonucleotides to unmodified siRNA molecules and teaches that siRNA molecules were preferred and thus one would not incorporate modifications. Applicant inserts their own interpretation of the Elbashir et al. reference, which is addressed above. Simply because unmodified siRNA molecules were better than modified antisense oligonucleotides does not mean that one of skill would not want to further enhance the stability of the siRNA molecule via incorporating modifications. One of skill in the art would not assume that siRNA molecules do not face stability challenges at all given that any exogenous nucleic acid would. Furthermore, Bertrand specifically teaches that "Consequently, it seems on this example in cell culture that the essential question of intracellular delivery is very similar for ODNs and siRNAs and that many results already obtained with ODNs within the last 20 years could now be improved using siRNAs in the same conditions of delivery into cells." (see page 1003, column 1). Therefore, Bertrand specifically sets forth the issue of delivery and teaches that siRNAs should be used in the same conditions that ODNs had previously been used.

Applicant points to *KSR International Co. v. Teleflex Inc.* (127 S. Ct. 1727 (2007)) to argue that the instant claims are directed to a new combination wherein the result cannot be predicted. As explained above, the instant claims are directed to a huge genus of modifications and combinations thereof, wherein the schematic is entirely target sequence specific. One would have been motivated to combine the prior-art

elements and expect active molecules within the instant claim breadth. It is well within the grasp of the skilled artisan to select and combine known elements within the instant huge genus and to expect active molecules upon routine optimization of the placement of such modifications given the teachings in the nucleic acid inhibitor art. It is the routine optimization of the placement of the modifications that is relied upon for determining activity of such molecules, as it was known to perform such routine testing, as evidenced by the instant references.

In view of *KSR International Co. v. Teleflex Inc.*, when a combination of admittedly old elements produces a new and beneficial result never attained before, it is evidence of invention. However, in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art.

Applicant argues that some direction in the prior art that would provide a reasonable expectation of success is required. IT is believed that the examiner has explained the teaching of the prior art and how these teachings would result in a reasonable expectation of success within the instant genus, which again only requires 2 more modifications than Elbashir et al. The instant types of modifications were routinely used in the nucleic acid inhibitor art.

Applicant points to specific species within the instant genus in the instant specification and compares the molecules to those of Elbashir et al. Again, the instant genus is huge depending on the target sequence and combination/quantity of each type

of the instants modifications. Applicant is pointing to species that are not representative of the instant genus and do not represent unexpected results for the instant genus.

Armed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules. The unmet need, as required by KSR, is that of balancing stability and activity with known chemical modifications.

Although applicant asserts that the instant claims require specific combinations of modifications at specific positions, the instant claims recite multiple types of modifications that can be incorporated alone or in various combinations with other modifications, rather than any one specific combination of modifications that have shown some unexpected property. Furthermore, the only positions that are specified are purines vs pyrimidines, of which there are only two choices for the skilled artisan to incorporate modifications at. The claims are not directed to any specific target sequence and therefore the incorporation at purines or pyrimidines varies depending on the specific target sequence. Therefore, each of these elements is variable rather than directed to a specific configuration as asserted by applicant.

The references collectively set forth that each of the instant types of chemical modifications were routinely incorporated into various types of inhibitory nucleic acid molecules (ribozymes, antisense, dsRNA, or siRNA molecules); that it was known to utilize the same types of chemical modifications from one nucleic acid chemistry to the

other, as each faces similar delivery challenges; it was known to optimize such molecules via testing different combinations or locations of incorporation; and it was known to target genes in a sequence specific fashion. The modifications of Parrish et al. are specific to pyrimidines. Furthermore, as explained in the rejection under 35 USC 103(a) above, there are a finite number of choices for positions of incorporation (purine or pyrimidine).

The majority of applicant's arguments appear to be upon the assumption that the instant claims are closed to a specific pattern. However, this is not the case. Although applicant asserts that a specific pattern is being claimed, the instant genus is very large, wherein applicant has not demonstrated any unexpected property of such a large genus given the motivation in the prior art to incorporate the same types of modifications, wherein the modifications would necessarily need to be incorporated into purines or pyrimidines.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/170,290. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '290 are specific for a BACE gene, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/185,652. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '652 are specific for a human c-Fos RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/204,572. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '572 are specific for a human ECGF1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/203,055. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '055 are specific for a human VCAM-1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/200,736. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '736 are specific for a Cyclin D1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/203,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '731 are specific for a human CHRM3 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/204,612. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '612 are specific for a human MMP13 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/175,367. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '367 are specific for a human HIF1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 129-138 of copending Application No. 10/444,853. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are directed to double stranded nucleic acid molecules with substantially similar and overlapping structural characteristics, wherein the instant claims do not recite a target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requests that the double patenting rejection be held in abeyance.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on (571) 272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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